Remarks/Arguments

The present amendment accompanies a Petition for the Revival of an Application Abandoned Unintentionally under 37 CFR §1.137(b) and is responsive to the Office Action mailed on March 26, 2003. Claims 1-14 currently are pending. In the Office Action, the Examiner rejected claims 1, 2 and 4-13 under 35 U.S.C. §112, first paragraph, claims 1-13 under 35 U.S.C. §112, second paragraph and claims 1-8 and 10-13 under 35 U.S.C. §102(e) and (b). The Examiner allowed claim 14 for which Applicants express their appreciation. In view of the discussion set forth below, Applicants request reconsideration and withdrawal of the rejections.

Rejections under 35 U.S.C. §112, first paragraph

Claims 1, 2 and 4-13 stand rejected under 35 U.S.C. §112, first paragraph for reasons set forth in Examiner's Paper No. 10, page 2-5, point 5. Generally, the Examiner has asserted that the written description is not commensurate in scope with the claims and that the specification only supports one mutant polypeptide consisting of 166 amino acids defined as SEQ ID NO:2. The Examiner further has asserted that "There is no disclosure, beyond the mere mention of possible other mutants is made in the specification" (Examiner's Paper No. 10, page 4, last paragraph).

Applicants respectfully traverse the rejection. To meet the requirements of 35 U.S.C. §112, first paragraph, an Applicant's specification must contain "a written description of the invention and the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same." (35 U.S.C. §112) Applicants respectfully submit that they have provided sufficient written description of the invention as to reasonably convey to those of ordinary skill in the art at the time the invention was filed that theyhad possession of the claimed invention.

As the specification states, Applicants' invention relates to mutant Bcl-2 proteins derived from wild-type or naturally occurring human Bcl-2. More specifically, the specification teaches that these mutant Bcl-2 proteins have a sequence of the amino acid residues (which form its unstructured, flexible loop) replaced with at least 4 to about 50 amino acid residues of which at least two are acid amino acids (page 7, lines 11-15). The

specification also teaches that the acidic amino acids may be located in any position within the replacement sequence and that the replacement sequence may comprise only one type of acidic residue or a combination of both (page 7, lines 15-17). It further teaches that there is no limit on the type or total number of acidic amino acids comprising the replacement sequence, as long as it comprises at least 2 (page 7, lines 18-20). It also teaches that that the proteins can contain from about 150-180 amino acid residues (page 7, line 31, continuing to page 8, line 1). In effect, the specification not only teaches the size range and makeup of the replacement sequence (i.e. any amino acid residues, of any type, in any order, as long as at least two of them are acidic) but also the size range of the mutant proteins. Accordingly, the specification provides adequate written description of the claimed invention.

Claims 1, 2 and 4-13 also stand rejected under 35 U.S.C. §112, first paragraph as being non-enabled. The Examiner has asserted that the polypeptide having the amino acid sequence of SEQ ID NO:2 comprising SEQ ID NO:1 does not reasonably provide enablement for the myriad of variant polypeptides embraced by the claims. The Examiner has asserted that proteins containing at least a portion of a flexible loop from human Bcl-x_L may not maintain the activities proposed in the specification. The Examiner also concluded that the predictability of changes to the amino acid sequence is practically nil. (Examiner's Paper No. 10, page 5-7, point 6)

Applicants respectfully traverse the rejection. To meet the requirements of 35 U.S.C. §112, first paragraph, an Applicant's specification must provide a teaching of how to make and use the invention. Applicants respectfully submit that the present specification thoroughly complies with this legal requirement.

Applicants' believe that a brief summary of their invention will assist the Examiner in understanding their position. Applicants' specification teaches that the claimed mutant Bcl-2 proteins are ones wherein a sequence of amino acids comprising the native Bcl-2 flexible loop have been replaced with at least 4 to about 50 amino acid residues of which at least two are acidic amino acids. The addition of at least 2 acidic amino acids in the modified flexible loop lowers the isoelectric point of the mutant protein to a level below that of wild-type Bcl-2. As a result of having a lowered isoelectric point, the mutant proteins of the invention do not aggregate in solution. This property allows them to be used for their intended purpose, namely, in X-ray crystallography and NMR studies as well as in assays to identify candidate

compounds which block the ability of Bcl-2 to inhibit programmed cell death. (Pages 5-6, bridging paragraph). The specification further teaches that wild-type Bcl-x_L contains an unstructured flexible loop which is neither required for maintaining the integrity of the protein in solution nor for retaining its function as an anti-apoptotic protein (page 7, lines 2-7). Based on sequence homology between Bcl-x_L and Bcl-2, the unstructured loop of Bcl-2 also is presumed to be unnecessary for maintaining the integrity of the Bcl-2 protein (page 7, lines 7-9)

In view of this background, it is Applicants' position that their specification fully enables the claimed invention. The specification provides sequence information for three different isoforms of Bcl-2 (see e.g. Figure 1) and identifies the general region of the flexible loop. The specification also teaches the make-up of the replacement sequences (page 7, lines 11-20), a specific replacement sequence (e.g. SEQ ID NO:1) and the sequences of a Bcl2/iso1 and Bcl-2/iso2 mutants (Example 1). The specification further provides that the mutant proteins of the invention can be prepared using techniques known in the art, such as by recombinant DNA techniques and purified by a number of chromatographic procedures (page 9, line 26 continuing through page 12, line 14 and Example 1). Finally, the specification teaches screening assays using the proteins of the invention (page 9, line 26 continuing through page 12, line 14 and Example 2). Accordingly, the specification adequately teaches how to make and use the claimed proteins.

Rejections under 35 U.S.C. §112, second paragraph

Claims 1-13 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner has asserted that "the loop is essential to the wild-type and mutant human Bcl-2 proteins, however it is not clear what defines the loop, i.e. amino acid residues, structural juxtaposition." (Examiner's Paper No. 10, page 7, point 8(a)) The Examiner requested further clarification.

Applicants respectfully traverse the rejection on several grounds. First, as mentioned in Applicants' specification, the sequence of wild-type Bcl-2 was known to those of ordinary skill in the art and had been described in several publications (See Applicants' specification, page 6, lines 17-28). Second, the specification describes a flexible loop as a sequence of

amino acids in a protein that shows no regular secondary structure such as an α-helix or β-sheet (page 7, lines 3-4 and Figures 1, 2 and 3). Accordingly, the flexible loop is clearly defined.

The Examiner also deemed claim 2 to be vague and indefinite as "it is not clear how many amino acids coding for the flexible loop would be necessary to maintain structure and function." (Examiner's Paper No. 10, page 7, point 8(b)). As Applicants stated above, the specification teaches that the flexible loop of Bcl-x is not required either for maintaining the integrity of the protein or retaining function. Due to sequence homology, the same is presumed true for the Bcl-2 flexible loop. Accordingly, those of ordinary skill in the art would fully understand the metes and bounds of the invention.

Rejection under 35 U.S.C. §102(e)

Claims 1-8 and 10-13 stand rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent NO. 6,214,986 (filing date June 2, 1999). The Examiner has asserted that Sequence 2 in columns 51 and 53 of the patent discloses a human mutant protein derived from wild-type human Bcl-2. The Examiner further referred to Sequence 2 in an attached database sheet, which the Examiner alleges shows the replacement amino acid sequence comprising at least 16 amino acid residues of Applicant's SEQ ID NO:1. The Examiner also stated that "It is reasonable to conclude the anticipatory mutant protein would have an isoelectric point lower than that of wild-type Bcl-2, wherein it is from 4.5 to about 6.0." (Examiner's Paper No. 10, page 8, point 10)

Applicants respectfully traverse the rejection. To anticipate the present invention, the disclosure of U.S. Patent No. 6,214,986 must both teach and enable Applicants' invention as presently claimed. Contrary to the Examiner's position, SEQ ID NO:2 of U.S. Patent No. 6,214,986 does not disclose a mutant protein as claimed by Applicants, but rather only the wild-type sequence of Bcl-x_L.

Unlike the '986 patent, Applicant's invention is not directed to Bcl-x_L but to a mutant protein of Bcl-2 in which the Bcl-2's unstructured, flexible loop is replaced with at least 4 to about 50 amino acids of which at least two are acidic amino acids (page 7, lines 12-14 and claim 1). In a preferred embodiment, this unstructured, flexible loop is replaced with a sequence of at least 4 to 50 amino acid residues corresponding to a contiguous sequence of

amino acid residues from the unstructured loop of Bcl-x_L, of which at least two are acidic amino acids (page 7, lines 21-24). Nothing in the '986 patent specification either teaches, suggests or enables a mutant protein derived from a wild-type Bcl-2 protein comprising a flexible loop structure as recited in Applicants' claims. In addition, nothing in the '986 patent specification either teaches, suggests or enables a mutant Bcl-2 protein comprising an isoelectric point lower than that of wild-type Bcl-2.

Furthermore, the database sequence generated by the Examiner merely shows a sequence alignment between Applicants' claimed invention (top strand) and the wild-type Bcl-x_L protein (lower strand, SEQ ID NO:2 of the '986 patent). As noted above, SEQ ID NO:2 is not a disclosure of the claimed invention but merely the sequence of wild-type Bcl-x_L. Accordingly, U.S. Patent 6,214,986 cannot anticipate the present invention.

Rejections under 35 U.S.C. §102(b)

Claims 1-8 and 10-13 stand rejected under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 5,646,008. The Examiner has asserted that SEQ ID NO:7 in columns 53 and 54 disclose a mutant wild-type human Bcl-2 protein which contains a replacement amino acid sequence comprising at least two acidic amino acids instead of the wild-type's amino acid residues corresponding to a flexible loop. (Examiner's Paper No. 10, page 9, point 11). The Examiner further stated that "it is reasonable to conclude the anticipatory mutant protein would have an isoelectric point lower than that of wild-type Bcl-2, wherein it is from 4.5 to about 6.0.

Applicants respectfully traverse the rejection. Contrary to the Examiner's assertion, SEQ ID NO:7 of the '008 patent is not a mutant Bcl-2 protein, but rather a mutant Bcl-x_L protein in which approximately 63 out of 233 total amino acids of the wild-type Bcl-x_L molecule have been deleted. The deleted residues do not reside in the flexible loop region of the Bcl-x_L protein. There is no disclosure whatsoever in the '008 patent that either teaches, suggests or enables a mutant protein derived from a wild-type Bcl-2 protein comprising a flexible loop structure that has been replaced with at least 4 to about 50 amino acids of which at least two are acidic amino acids. In addition, nothing in the '008 patent specification either teaches, suggests or enables a mutant Bcl-2 protein comprising an isoelectric point lower than that of wild-type Bcl-2.

In addition, the database sequence generated by the Examiner merely shows a sequence alignment between Applicants' claimed invention (top strand) and the mutant Bcl-x_L protein (lower strand, SEQ ID NO:7 of the '008 patent). As noted above, SEQ ID NO:7 is not a disclosure of the claimed invention but merely of the sequence of a deletion mutant of Bcl-x_L (which deletion does not occur in the flexible loop). Accordingly, the U.S. Patent 5,646,008 cannot anticipate the claimed invention.

Claims 1-8 and 10-13 stand rejected under 35 U.S.C. §102(b) as being anticipated by Boise *et al.* (Cell 74: 597-608, August 27, 1993/IDS Reference C3). The Examiner has asserted that Figure 3 of the Boise reference discloses a human Bcl-x_L mutant protein. The Examiner further stated that "it is reasonable to conclude the anticipatory mutant protein would have an isoelectric point lower than that of wild-type Bcl-2, wherein it is from 4.5 to about 6.0. (Examiner's Paper No. 10, page 9, point 12)

Applicants respectfully traverse the rejection and submit that the Examiner has misunderstood the teachings of the reference with respect to their invention. Figure 3 (page 599, column 2 of the reference) merely shows a sequence alignment between the predicted open reading frames of two distinct human cDNAs (bcl-x_L and bcl-x_s) and a wild-type Bcl-2. As the reference teaches, bcl-x_s is a deleted form of bcl-x_L in that it lacks 63 amino acids of bcl-x_L. This deletion does not occur within the flexible loop of bcl-x_L. Nothing in this reference either teaches, suggests or enables a mutant Bcl-2 protein as presently claimed. In addition, nothing in the Boise reference either teaches, suggests or enables a mutant Bcl-2 protein comprising an isoelectric point lower than that of wild-type Bcl-2. Accordingly, the Boise *et al.* reference does not anticipate the present invention.

Claims 1-8 and 10-13 stand rejected under 35 U.S.C. §102(b) as being anticipated by Muchmore *et al.* (Nature 381:335-341, May 23, 1996/IDS reference C7). The Examiner has asserted that the Muchmore reference discloses a human Bcl-x_L mutant protein on page 337. The Examiner further stated that "it is reasonable to conclude the anticipatory mutant protein would have an isoelectric point lower than that of wild-type Bcl-2, wherein it is from 4.5 to about 6.0.

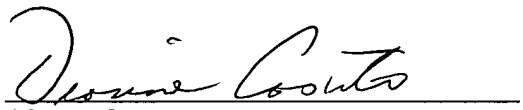
Applicants respectfully traverse the rejection and submit that the disclosure on page 337 of the Muchmore reference is merely a sequence alignment of wild-type Bcl-2 family members, including wild-type Bcl-x_L and wild-type Bcl-2. Muchmore *et al.* discuss deletion

mutants of Bcl-x_L (specifically, mutants having a deletion in the flexible loop and specifically, at positions 26-63 and 46-83) but simply conclude that such mutated proteins "retain anti-apoptotic function when overexpressed " (pages 338 and 339, bridging paragraph). Any disclosure relating to mutant Bcl-x_L is not a teaching, suggestion nor does it enable a mutant Bcl-2 protein as presently claimed. In addition, nothing in the Muchmore reference either teaches, suggests or enables a mutant Bcl-2 protein comprising an isoelectric point lower than that of wild-type Bcl-2. Accordingly, the Muchmore *et al.* reference does not anticipate the present invention.

Action Requested

Applicant respectfully asserts that in view of the above, they have overcome all outstanding rejections and request their withdrawal. Applicants also submit that the application is in condition for allowance and request passage to issue of the subject application. Should any issues remain, Applicants request that the Examiner contact the undersigned attorney to discuss same.

Respectfully submitted,
Stephen W. Fesik, et al.



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